PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
BCP103		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI2004/000717	26-11-2004	09-12-2003
International Patent Classification (IPC) or national classification and IPC		
See Supplemental Box		
Applicant		
Biocis Pharma Oy et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19-09-2005	20-02-2006
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Cover sheet

INTERNATIONAL PATENT CLASSIFICATION (IPC):

A61K 31/415 (2006.01)
A61P 35/00 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000717

Box No. I Basis of the report

1. With regard to the language, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-19 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 1-2 received by this Authority on 19-09-2005
pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-4 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000717

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☐ claims Nos. _____

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

Present claims 8-12 relate to a composition comprising an enhancer and an agent defined by reference to a desirable characteristic or property, namely "being able to acidify the

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III.2

cell cytoplasm" and a carrier defined as "which carrier essentially prevents the enhancer from dissociating at extracellular pH values". The claims cover all the compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful examination over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful examination over the whole of the claimed scope impossible.

Consequently, the examination has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the composition comprising cic-urocanic acid (UCA) and camptothecin.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000717

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims	1-7	YES
	Claims	8-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claimed invention in claims 1-7 relates to the use of cis-urocanic acid for the manufacture of a pharmaceutical composition for treating diseases or disorders connected to local or systemic cancer (see in particular page 4).

Claims 8-12 relate to a composition comprising a therapeutically active agent, an enhancer for said agent and an agent "being able to acidify the cell cytoplasm" and a carrier defined as "which carrier essentially prevents the enhancer from dissociating at extracellular pH values". In the present case, the claims lack support, and the application lacks disclosure.

Support and disclosure are found for those parts relating to a composition comprising cic-urocanic acid (UCA) and camptothecin.

Cited documents in the search report:

D1 Burobin V A; et al; "Biological activity of urocanic acid, being able to acidify the cell cytoplasm" and "for preventing or halting cellular proliferation in a person". Voprosy Meditsinskoi Khimii, (1985 Jan-Feb) 31 (1) 102-6, STN International Medline on STN, Medline AN:85169892, DN: 3984264.

D2 WO 2004/080456 A1 (published 23 September 2004)
D3 US 6028098 A1

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

D4 US 6372199 B1
D5 US 5995869 A1
D6 EP 612525 A1
D7 De 4121030 A1
D8 Goossens J-F; et al; "Relation between intracellular acidification and camptothecin-induced apoptosis in leukaemia cells", European Journal of Pharmaceutical Sciences 10 (2000) pages 125-131. (Cited in the application)

In D1, which is considered to represent the most relevant prior art, the biological activity of urocanic acid was studied in a culture of CaOV cell in vitro and in mice with transferred tumours in vivo. Urocanic acid inhibited the protein synthesis in tumour cells at the step of translation, retarding growth of various strains of transferring tumours in mice. Thus, urocanic acid can be used as an antitumoural drug.

In page 12 last paragraph in the application, it is stated "Although not yet studied in detail, the characteristics of UCA as a potential pharmacological substance in cancer intervention are promising".

The claimed invention in claims 1-7 differs from D1 in that it does not relate to cis-urocanic acid. The applicant has pointed out that cis-urocanic acid has advantages over trans-urocanic acid. Thus, claims 1-7 are novel and have inventive step.

Claims 8-9 and 12 relate to any compositions comprising a therapeutically active agent, an enhancer for said agent and a pharmaceutically acceptable agent being able to acidify the cell cytoplasm.

The claimed composition differs from D1 in that D1 only deals with urocanic acid.

The person skilled in the art is faced with the problem of providing a composition comprising a therapeutically active

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

agent, an enhancer for said agent and an agent "being able to acidify the cell cytoplasm" and a carrier defined as "which carrier essentially prevents the enhancer from dissociating at extracellular pH values". This problem is solved by using a composition comprising cic-urocanic acid (UCA) and camptothecin.

In D8, the use of camptothecin (CPT) for treating leukaemia is known. Incubation of the leukaemia cells with a high drug concentration for 5 h or a lower drug concentration for 15 h results in a pronounced intracellular acidification.

Considering what is known from D1 and D8, it is considered to lie within the skills of a person skilled in the art to prepare a composition comprising the known compounds and reach the claimed purpose. Thus, claims 8-12 lack inventive step.

The use and the effect of the combination of the compounds mentioned in claims 8-12, for example for treating or preventing cancer and hyperproliferative diseases, have not been shown for the whole scope of the claims, only for the combination of cic-urocanic acid (UCA) and camptothecin. Thus, claims 8-12 lack inventive step.

D2, which was published on 23 September 2004 with a claimed priority from 14 March 2003, discloses a pharmaceutical composition for intracellular acidification with cis-urocanic acid.

D3-D7 disclose the general state of the art and are not considered to be particularly relevant.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expressions "being able to acidify the cell cytoplasm" and "which carrier essentially prevents the enhancer from dissociating at extracellular pH values" in claims 8-9 and 12 relate to a large and undefined number of different compounds which cannot be clearly defined by these expressions. The application provides support for use of the compounds in the treatment of only a very limited number of such disorders.

Claims 8-9 and 12 relate to any compositions comprising a therapeutically active agent, an enhancer for said agent and a pharmaceutically acceptable agent being able to acidify the cell cytoplasm. Claims 8-9 and 12 do therefore not meet the requirements of Article 6 PCT that claims shall be clear, concise and supported by the description.

CLAIMS

1. Use of *cis*-urocanic acid for the manufacture of a pharmaceutical composition useful for preventing or halting cellular proliferation in a person or an animal, wherein an effective amount of said *cis*-urocanic acid is administered in an essentially non-dissociated form to the person or animal.

2. The use according to claim 1 wherein the agent is an agent having its dissociation constant in the range 5.0 to 7.4, preferably in the range 6.0 to 7.3; most preferably about 7.0.

3. The use according to any of the claims 1 to 2 for treatment or prevention of a disease or disorder curable by intracellular acidification inducing the inhibition or halting of cell proliferation.

4. The use according to claim 3 wherein the disease or disorder is a local or systemic, non-transformed or transformed hyperproliferative disease.

5. The use according to claim 4 wherein the disease or disorder is a local or systemic cancer selected from brain, lung, skin, bladder, gastric, pancreatic, breast, head, neck, kidney, ovarian, prostate, colorectal, oesophageal, gynaecological and thyroid cancer.

6. The use according to any of the foregoing claims wherein the *cis*-urocanic acid is administered systemically or locally, preferably locally, most preferably topically.

7. Use of cis-urocanic acid according to any of the claims 1 to 5, as an enhancer for another therapeutically active agent.

8. Pharmaceutical composition comprising a therapeutically active agent, an enhancer for said agent and a pharmaceutically acceptable agent being able to acidify the cell cytoplasm, in combination with a pharmaceutically acceptable carrier, which carrier essentially prevents the enhancer from dissociating at extracellular pH values.

9. The composition according to claim 8 wherein said enhancer is an agent having its dissociation constant in the range 5.0 to 7.4, preferably in the range 6.0 to 7.3; most preferably about 7.0.

10. The composition according to claim 8 or 9, wherein said enhancer is *trans*-urocanic acid.

11. The composition according to claim 8 or 9, wherein said enhancer is *cis*-urocanic acid.

12. The composition according to any of the claims 8 to 11, wherein the therapeutically active agent is an anti-proliferative or anticancer agent.